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(54) IMPROVEMENTS IN PHARMACEUTICAL FORMULATIONS

(71) We, ASPRO-NICHOLAS LIMITED, a British company, of 225 Bath Road, Slough, Buckinghamshire, England, and formerly of 16 Berkeley Street, London, W.1, England, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a process for preparing particles of paracetamol, the particles so produced and pharmaceutical compositions containing said particles.

Paracetamol (p-hydroxyacetanilide) has been used for a number of years as an analgesic and anti-pyretic. It is known, however, that when paracetamol comprises a major proportion of a pharmaceutical tablet—the form in which it is most frequently used—its tabletting characteristics are such as to produce unreliable results. Thus, for example, conventional tabletting procedures often produce tablets which are too soft and easily broken or the tablets are exceedingly slow to disintegrate. In addition, the tablets sometimes "stick" or "cap" in the tabletting machines. These and other problems make paracetamol a difficult substance to tablet especially in high speed tabletting machines and not infrequently results in large numbers of tablets being rejected with the subsequent expense of regranulation before a further attempt at tabletting may be made.

It is therefore, an object of the present invention to provide a coated paracetamol in such a form that it may be tabletted substantially without the problems associated with tabletting untreated paracetamol. It is a further object of the invention to provide a process for preparing such a coated paracetamol in a form suitable for direct compression into tablets which process avoids the granulation step or steps necessary in known methods of tabletting paracetamol. A still further object of the invention is to provide an improved pharmaceutical tablet comprising said coated paracetamol.

According to the present invention, there is provided a process for preparing coated paracetamol particles comprising agitating particles of paracetamol and a binding agent in an aqueous medium to form a slurry and thereafter drying the resultant slurry to obtain discrete particles of paracetamol coated with said binding agent, the amount of binding agent being such that the dried particles are coated with from 2 to 5%, preferably 3 to 4%, by weight of said binding agent and the ratio by weight of uncoated particles of paracetamol to the water in said medium being not greater than 5:1.

Although not less than one part of water to five parts of paracetamol may be used in the process of this invention, greater quantities of water may of course be used and indeed are preferable to ensure even coating. However, if too great an excess of water is used, the process becomes less economic since substantially all the water must be removed during the second, drying stage of the process. Accordingly, the preferred ratio by weight of paracetamol to water is from 3:1 to 1:3 and most advantageously from 2:1 to 1:1.

To achieve drying in the form of discrete particles, the slurry is dried in such a way that the coated particles are substantially prevented from forming large agglomerates by surrounding them with a warm gaseous atmosphere, normally air.

Preferred ways of drying to achieve the aforementioned effect are fluid-bed drying where essentially the coated particles are separated by passage of warm air through them and, most advantageously, spray-drying where the coated particles are separated by passage through a current of hot air. This latter method produces coated particles of

fairly uniform particle size, which are very free flowing and readily tabletted.

The particles of paracetamol prior to coating in accordance with the present invention should preferably be of such a size that all will pass through a 25 mesh B.S.S. screen and that at least 50% by weight will pass through a 350 mesh screen. Advantageously all the uncoated particles will pass through a 60 mesh screen and at least 70% — most advantageously 85%—by weight will pass through a 350 mesh screen.

The uncoated particles of paracetamol may be added to a solution or dispersion of the binding agent, or *vice versa,* or the paracetamol and binding agent may be added together to water. Preferably, in large scale production, the binding agent and a portion of the paracetamol are added with agitation to the water and, after initial mixing, the remaining portion or portions of paracetamol are added. To ensure that the binding agent is evenly distributed around the paracetamol particles, agitation is preferably carried out using a high shear mixer. The temperature at which slurrying is carried out is not critical but is dependent on the binding agent used.

The binding agents used in the process of the present invention comprise pharmaceutically acceptable substances capable of dispersing in an aqueous medium, of forming a film on the paracetamol particles, and of assisting adherence of the coated particles after compression into tablets. Suitable binding agents include those hitherto used in pharmaceutical formulations such as sugars for example sucrose, molasses and lactose, and natural and synthetic gums for example, acacia, tragacanth, sodium alginate, carboxymethylcellulose, methylcellulose and polyvinylpyrrolidone. Preferred as binding agents of this invention are gelatin and derivatives thereof including cold water soluble protein materials derived hydrolytically from gelatin. Particularly useful examples of the latter materials are those known at the date hereof under the trade names BYCO-C and BYCO-D (available from B. Young & Co. Ltd., 168/173 High Holborn, London, W.C.1.). The latter compounds are white powders having an average bulk density of 0.34 g./cc. and average particle size of 23 microns. Analysis thereof reveals that they contain from 5 to 6% by weight of moisture and have a nitrogen content of from 15.5 to 16.5% by weight. The viscosity of a 10% by weight solution in water of the materials is from 40 to 50 millipoises. They are produced under conditions such that they are substantially free from micro-organisms and thus are particularly useful in minimising growth in formulations containing these compounds.

The coated paracetamol particles of the present invention are a novel composition of matter and accordingly form a part of this invention. They may be used as all or part of the paracetamol content of a pharmaceutical composition together with a pharmaceutically acceptable carrier therefor and accordingly such compositions are also a part of this invention. One or more other active ingredients may be included in such compositions, for example, salicylamide and/or caffeine, codeine phosphate, butobarbitone, dexamphetamine, dextropropoxyphene, chloral hydrate, chlormezanone, aspirin, orphenadrine, phenylbutazone, meprobamate, phenylpropanolamine, phenyltoloxamine, mepyramine, homatropine or ethoheptazine. Such pharmaceutical composition may be in effervescent form.

The full advantage of the use of the coated paracetamol particles of the invention is realised in the preparation of pharmaceutical tablets, particularly those where paracetamol is the major active ingredient, since the coated particles may satisfactorily be directly compressed into tablets at high speed and without the occurrence of the problems mentioned above which may be encountered in tabletting paracetamol. Accordingly, tablets comprising such coated particles form a preferred feature of this invention. Such tablets, in their ease and reproducibility of manufacture and in their physical characteristics, show a marked improvement over prior art paracetamol tablets.

The following Examples will further illustrate the invention:—

EXAMPLE 1

2 Kilos of Byco-C soluble protein and 11 kilos of paracetamol (of a particle size such that all the particles passed through an 85 mesh B.S.S. screen and 85% by weight of them passed through a 350 mesh B.S.S. screen) were added to 34 litres of cold water contained in a high shear mixer of 120 litre capacity. After the initial mixing had been completed, 3×13 kilos of the paracetamol were added in separate batches while mixing continued. The slurry produced, containing 50 kilos of the paracetamol and 2 kilos of the Byco-C soluble protein, was strained and transferred to a vessel with a gate-type agitator. From this vessel the slurry was pumped to the spray-head of a spray-drier and dried at an air temperature of 75 to 90°C. The resultant particles of paracetamol coated with 4% by weight of Byco-C soluble protein were of substantially uniform particle size and very free flowing. They could be directly compressed into satisfactory tablets.

Similar results were obtained when 50 kilos of warm water and 1.5 kilos of gelatin were used.

EXAMPLE 2

Gum acacia (500 g.) was dissolved in 20 litres of water and 2×5 kilos of paracetamol (particles size as in Example 1) was added with

vigorous agitation. The slurry produced was strained and, with continuous agitation, was fed to a spray drier to be dried at an air temperature of 80 to 90°C. The resultant particles of paracetamol were coated with 5% by weight of gum acacia.

Similarly using polyvinylpyrrolidone (350 g.) in place of the gum acacia and 10 litres of water, there was obtained free flowing particles of paracetamol coated with 3.5% by weight of polyvinylpyrrolidone.

EXAMPLE 3

Using the process of Example 1 but with 30 kilos of paracetamol, 1 kilo of lactose and 15 litres of warm water, there were obtained paracetamol granules coated with 3.3% by weight of lactose.

EXAMPLE 4

Tablets each containing the following ingredients were prepared

Paracetamol particles coated with 4% by weight of BYCO-C	520 mg.
Maize Starch	44 mg.
Pre-gelatinized Starch	24 mg.
Stearic Acid	6 mg.
Talc	6 mg.
TOTAL	600 mg.

The coated paracetamol was dry blended with the other ingredients and compressed into tablets at a rate of 300,000 per hour per machine. The tablets produced were free of physical defects, were of adequate hardness and had a disintegration time of less than 2 minutes (15 minutes being allowed in accordance with the British Pharmacopoeia specification). Similar tablets were prepared using other coated paracetamols described in Examples 1 to 3.

EXAMPLE 5

Satisfactory tablets were prepared using the same excipients as in Example 4 but containing, as active ingredients, paracetamol particles coated with 3% by weight of gelatin—250 mg., salicylamide—250 mg. and caffeine—25 mg.

The tablets of this and the previous Example may alternatively be formulated with an effervescent base using methods well known in the art.

WHAT WE CLAIM IS:—

1. Process for preparing coated particles of paracetamol which comprises agitating particles of paracetamol and a binding agent in an aqueous medium to form a slurry and thereafter drying said slurry to obtain discrete particles of paracetamol coated with from 2 to 5% by weight of said binding agent, the ratio by weight of the particles of paracetamol prior to coating to the water in said aqueous medium being not greater than 5:1 and said binding agent being selected from pharmaceutically acceptable substances capable of dispersing in an aqueous medium, forming a film on the paracetamol particles and assisting adherence of the coated particles after compression into tablets.

2. Process as claimed in Claim 1, wherein said binding agent is a sugar, a natural or synthetic gum, or gelatin or a derivative thereof.

3. Process as claimed in Claim 2, wherein the said derivative of gelatin is a cold water soluble protein material derived hydrolytically from gelatin.

4. Process as claimed in Claim 3, wherein the said protein material is that known at the date hereof under the trade name BYCO-C or BYCO-D.

5. Process claimed in any one of the preceding Claims, wherein the ratio by weight of paracetamol prior to coating to the water is from 3:1 to 1:3.

6. Process as claimed in any one of the preceding Claims, wherein the coated particles are dried in a manner such that the formation of large agglomerates is substantially prevented by surrounding them with a warm gaseous atmosphere.

7. Process as claimed in Claim 6, wherein the coated particles are fluid-bed dried or spray-dried.

8. Process as claimed in any preceding Claim, wherein the paracetamol particles prior to coating are of such a size that all will pass through a 25 mesh B.S.S. screen and that at least 50% by weight of them will pass through a 350 mesh B.S.S. screen.

9. Process as claimed in Claim 8, wherein all of the paracetamol particles prior to coating will pass through a 60 mesh B.S.S. screen and at least 70% by weight will pass through a 350 mesh B.S.S. screen.

10. Process for preparing coated particles of paracetamol which comprises spray-drying a slurry which has been formed by agitating in an aqueous medium particles of paracetamol of such a size that all will pass through a 60 mesh B.S.S. screen and at least 70% by weight will pass through a 350 mesh B.S.S. screen, and from 2 to 5% by weight of a cold water soluble protein material derived hydrolytically from gelatin, the ratio by weight of said paracetamol to the water in the slurry being from 3:1 to 1:3.

11. Process for preparing coated particles of paracetamol substantially as described with reference to any one of Examples 1 to 3.

12. Discrete paracetamol particles coated with from 2 to 5% by weight (on a dry basis) of a binding agent selected from pharmaceutically acceptable substances cap-

able of dispersing in an aqueous medium, of forming a film on the paracetamol particles, and of assisting adherence of the coated particles after their compression into tablets.

13. Paracetamol particles as claimed in Claim 12, wherein said binding agent is a sugar, a natural or synthetic gum, or gelatin or a derivative thereof.

14. Paracetamol particles as claimed in Claim 13, wherein the said derivative of gelatin is a cold water soluble protein material derived hydrolytically from gelatin.

15. Paracetamol particles as claimed in Claim 14, wherein the said protein material is that known at the date hereof under the trade name BYCO-C or BYCO-D.

16. Paracetamol particles whenever prepared by a process as claimed in any one of Claims 1 to 11.

17. Pharmaceutical composition comprising as an active ingredient paracetamol particles as claimed in any one of Claims 12 to 16 together with a pharmaceutically acceptable carrier therefor.

18. Composition as claimed in Claim 17, wherein the composition contains one or more other pharmacologically active ingredients.

19. Composition as claimed in Claim 18, wherein the composition contains salicylamide and caffeine as other pharmacologically active ingredients.

20. Composition as claimed in any one of Claims 17 to 19, in effervescent form.

21. Composition as claimed in any one of Claims 17 to 20, in tablet form.

22. Pharmaceutical tablets substantially as described with reference to Example 4 or Example 5.

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